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Lactic Acidosis During Sepsis Is Related to Increased Pyruvate Production, Not Deficits in Tissue Oxygen Availability

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Objective

The purpose of this study was to quantitate the derangements in intermediary carbohydrate metabolism and oxygen use in severely septic patients in comparison with healthy volunteers.

Summary Background Data

It commonly has been assumed that the development of lactic acidosis during sepsis results from a deficit in tissue oxygen availability. Dichloroacetate (DCA), which is known to increase pyruvate oxidation but only when tissue oxygen is available, provides a means to assess the role of hypoxia in lactate production.

Methods

Stable isotope tracer methodology and indirect calorimetry was used to determine the rates of intermediary carbohydrate metabolism and oxygen use in five severely septic patients with lactic acidosis and six healthy volunteers before and after administration of DCA.

Results

Oxygen consumption and the rates of glucose and pyruvate production and oxidation were substantially greater ($p < 0.05$) in the septic patient compared with healthy volunteers. Administration of DCA resulted in a further increase in oxygen consumption and the percentage of glucose and pyruvate directed toward oxidation. Dichloroacetate also decreased glucose and pyruvate production, with a corresponding decrease in plasma lactate concentration.

Conclusions

These findings clearly indicate that the accumulation of lactate during sepsis is not the result of limitations in tissue oxygenation, but is a sequelae to the markedly increased rate of pyruvate production. Furthermore, the substantially higher rate of pyruvate oxidation in the septic patients refutes the notion of a sepsis-induced impairment in pyruvate dehydrogenase activity.

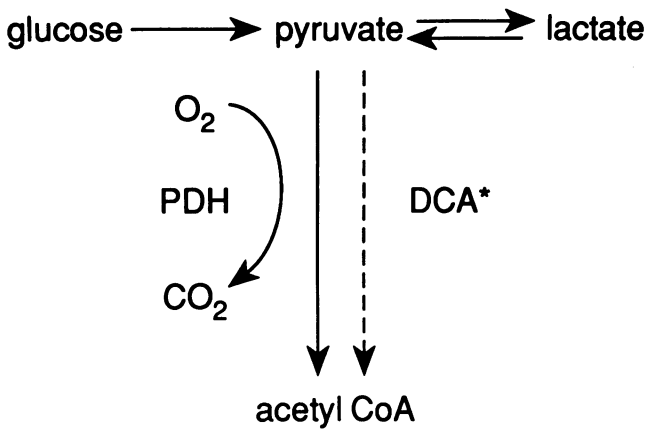

Figure 1. Intermediary carbohydrate metabolism. The rate of oxidative decarboxylation of pyruvate is accelerated by dichloroacetate (DCA), but only when sufficient oxygen is available.

Increasing severity of sepsis is hallmarked by a progressive elevation in lactic acid. Because a central feature of sepsis is inadequate tissue perfusion, it commonly is assumed that the increased lactate production results from a deficit in oxygen availability.[1,2] That pyruvate is preferentially shunted to lactate because it cannot be promptly oxidized. In contrast to this prospective, several recent studies have suggested that lactic acidosis during critical illness primarily is the result of an increased rate of glycolysis coupled with a limitation in pyruvate dehydrogenase activity.[3,4] This hypothesis implies that tissue hypoxia may not be the rate determining factor for lactate production during sepsis.

Dichloroacetate (DCA) provides a means to test the role of hypoxia in lactate production. Under normal physiologic conditions, DCA stimulates pyruvate dehydrogenase activity, with a resultant increase in pyruvate oxidation.[5] This increase in pyruvate oxidation is dependent on adequate tissue oxygenation. Therefore, if oxygen deficiency is the primary component for the increased lactate production during sepsis, DCA should have no effect on the rate of pyruvate oxidation or tissue oxygen use. However, if lactate production is primarily the result of an acceleration in glucose/pyruvate/lactate flux, then DCA should decrease lactate production by increasing the rate of pyruvate oxidation (Fig. 1).

To evaluate the role of tissue oxygenation and intermediary carbohydrate metabolism in the etiology of lactic acidosis during sepsis, the human *in vivo* kinetics of glucose, pyruvate, lactate, and oxygen use were measured before and after DCA administration in five patients with terminal sepsis and severe lactic acidosis using a primed, continuous infusion of 6,6d_2 glucose, 1^{13}C pyruvate, and indirect calorimetry. For comparison, six healthy volunteers were studied in a similar fashion.

METHODS

Subjects

Five septic females (sepsis severity score ≥ 26)[6] with severe lactic acidosis (plasma lactate concentration ≥ 5.0 μmol/L per liter and arterial blood pH ≤ 7.35) participated in this study, as approved by the Institutional Review Broad of the Medical College of Virginia (Table 1). Because of the inability to obtain informed consent personally from these severely ill patients, consent for study participation was obtained from the patients' next of kin. Patients were categorized as septic as defined by clinical parameters outlined by the recent consensus conference on the septic syndrome.[7] In addition, each patient had an overt septic focus with culture-positive bacterial infection. These patients were ventilated mechanically, heavily sedated or paralyzed, and with indwelling pulmonary artery catheter monitoring during study. Despite their wide range in age (20–76 years) and size (1.52–2.03 M^2 body surface area), all patients were markedly hyperdynamic, as evidenced by elevations in heart rate and cardiac index and an associated decrease in systemic vascular resistance (Table 2). Six healthy male volunteers of similar age and size also participated in this study (Table 1). The volunteers were considered healthy based on screening history, physical examination, and blood

Table 1. PATIENT DEMOGRAPHICS

	Volunteers	Septic Patients
Age (yr)	24 ± 1	46 ± 9
Weight (kg)	71.2 ± 1.8	80.0 ± 10.4
Body surface area (m^2)	1.69 ± 0.04	1.79 ± 0.09
APACHE III score	0	100 ± 11
Sepsis Severity Score	0	34 ± 2
Mortality (%)	0	100

Patient No.	Septic Focus	Cultures
1	Necrotizing fascitis right arm/chest wall	*Peptostreptococcus*
2	Multiple liver abscesses	*E. coli, Enterobacter cloacae*
3	Pancreatic abscess	*Xanthamonas multiphilia*
4	Multiple liver abscesses	*Pseudomonas aeruginosa*
5	Multiple intra-abdominal abscesses	*Klebsiella pneumonia*

APACHE = Acute Physiology and Chronic Health Evaluation.
Values for demographics are mean ± standard error of the mean.

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Table 2. HEMODYNAMIC AND OXYGEN UTILIZATION MEASUREMENTS IN SEPTIC PATIENTS (PULMONARY ARTERIAL CATHETER MONITORING)

	Basal	DCA
Heart rate (beats/min) (normal range 60–100)	116 ± 4	114 ± 4
Cardiac index (L/min/m^2) (normal range 3.0–4.0)	5.5 ± 0.9	5.6 ± 0.9
Systemic vascular resistance index (dyne · sec/cm^5/m^2) (normal range 770–1500)	402 ± 31	396 ± 28
Oxygen delivery (mL/min/m^2) (normal range 550–650)	663 ± 93	685 ± 66
Oxygen consumption (mL/min/m^2) (normal range 115–165)	120 ± 7	129 ± 9*
Oxygen extraction (%) (normal range 24–28)	21 ± 2	26 ± 2*

Values are mean ± standard error of the mean.
* $p < 0.05$ by Student's paired t test.

sampling. All were normal for height and weight and took no medications.

Study Protocol

For the septic patients, the study was initiated 6 hours after discontinuation of all nutritional supplementation, and dextrose was removed from the intravenous solutions. For the healthy volunteers, the study was started in the early morning after an overnight fast. The study protocol (Fig. 2) was otherwise identical for both patients and healthy volunteers and was initiated after baseline breath and arterial blood sampling. Then infusions of 6,6 d_2 glucose (0.333 μmol/L/kg per minute, 20 μmol/L/kg prime) and 1-^{13}C pyruvate (1.5 μmol/L/kg per minute, 22.5 μmol/L/kg prime) were given intravenously and continued for the duration of the 6-hour study. At 90, 105, and 120 minutes of isotopic glucose and pyruvate infusion, breath and arterial blood sampling was repeated (basal period). Each subject then received two 30-minute intravenous infusions of DCA (1.2 mg/kg per minute), separated by 90 minutes (total dose of DCA = 72 mg/kg). This dosage previously has been shown to significantly lower plasma lactate concentrations in healthy individuals.[3] Breath and blood sampling was repeated at 210, 225, and 240 minutes after the initial DCA infusion (DCA period). Oxygen consumption and resting energy expenditure were determined by indirect calorimetry with a metabolic cart (DeltraTrac, Sensormedics Inc., Anaheim, CA) used repeatedly during both basal and DCA periods.

Blood samples were analyzed for glucose, lactate, and pyruvate concentration by the oxidase method using an automated analyzer (YSI 2300 G/L analyzer, Yellow Springs Instrument Co., Yellow Springs, OH). Isotopic enrichments of glucose and pyruvate were determined by gas chromatography mass spectrometry after pentaacetate and pentafluorobenzyl derivitization, respectively.[8] Breath samples were analyzed for $^{13}CO_2$ enrichment by isotope ratio mass spectrometry.

Calculations

Analysis for isotopic enrichment on serial blood and breath samples collected during the final 30 minutes of both basal and DCA periods confirmed an apparent equilibrium with good plateau enrichments. Calculations for steady-state kinetics were employed using tracer/tracee ratio (Eq. 1). Glucose clearance rate was quantitated by dividing glucose Ra by the plasma concentration (Eq. 2) (Fig. 1).

$$\text{glucose Ra} = F(1/Ep) \quad (1)$$

$$\text{pyruvate Ra} = F(1/Ep)$$

$$\text{glucose CR} = \text{glucose Ra}/C \quad (2)$$

where glucose Ra = glucose production (μmol/kg/min); pyruvate Ra = pyruvate production (μmol/kg/min); F = isotopic infusion rate (μmol/kg/min); Ep = isotopic enrichment at plateau; glucose CR = glucose clearance rate (mL/kg/min); and C = arterial glucose concentration (mmol/L).

A Student's independent t test was used for statistical comparison between healthy volunteers and septic patients. A Student's paired t test was used for statistical comparison between basal and DCA period measurements for both study groups. Results are presented as mean ± standard error of the mean, and $p \leq 0.05$ was accepted as significant.

RESULTS

Oxygen consumption was elevated significantly in the septic patients in comparison with the healthy volun-

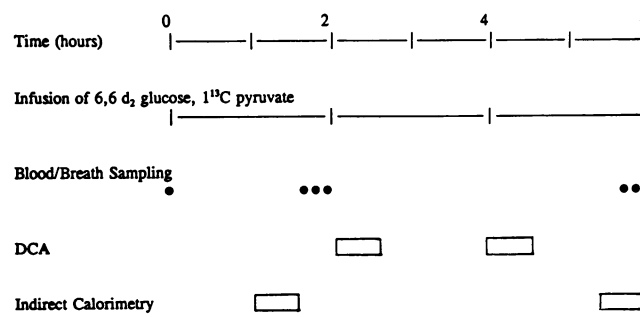

Figure 2. Study protocol flow diagram.

Table 3. COMPARISON OF GLUCOSE AND PYRUVATE KINETICS AND INDIRECT CALORIMETRY IN SEPTIC PATIENTS AND VOLUNTEERS

	Volunteers		Septic Patients	
	Basal	DCA	Basal	DCA
Substrate concentrations				
Glucose (mmol)	5.6 ± 0.1	5.5 ± 0.1	12.5 ± 3.2†	9.5 ± 2.6*
Pyruvate (μmol)	84 ± 25	38 ± 8*	387 ± 92†	299 ± 61*
Lactate (μmol)	1.5 ± 0.1	0.7 ± 0.1*	14.8 ± 3.3†	12.9 ± 2.4*
Glucose production (μmol/kg/min)	14.1 ± 0.3	12.7 ± 0.3*	42.3 ± 10.4†	31.2 ± 7.7*
Glucose oxidation (μmol/kg/min)	9.2 ± 2.2	10.2 ± 1.8	22.9 ± 3.0†	27.0 ± 3.7*
Glucose clearance (mL/kg/min)	2.5 ± 0.1	2.6 ± 0.1	3.5 ± 0.3†	3.5 ± 0.4
% glucose oxidized	65 ± 4	80 ± 3*	54 ± 6	87 ± 4*
Pyruvate production (μmol/kg/min)	34 ± 1	26 ± 6*	127 ± 28†	92 ± 21*
Pyruvate oxidation (μmol/kg/min)	19.4 ± 1.2	16.9 ± 1.0*	61.4 ± 14.0†	50.6 ± 4.1*
% pyruvate oxidized	57 ± 3	65 ± 4*	48 ± 7	55 ± 6*
Oxygen consumption (mL/min/m^2)	124 ± 9	136 ± 7	154 ± 11†	171 ± 19*

DCA = dichloroacetate.
Values are mean ± standard error of the mean.
* $p < 0.05$ *vs.* basal by Student's paired t test.
† $p < 0.05$ *vs.* volunteer basal by Student's independent t test.

teers, as measured by indirect calorimetry (Table 3). Elevations in oxygen delivery and a decreased fractional extraction of oxygen also was demonstrated in the septic patients, as facilitated by the pulmonary artery catheter (Table 2). The septic patients had significantly higher arterial plasma concentrations of glucose, pyruvate, and lactate than the healthy volunteers (Table 3). Furthermore, the rates of glucose and pyruvate production also were significantly elevated in the septic patients. However, because the absolute rates of glucose and pyruvate oxidation also were elevated markedly in the septic patients, the percentage of glucose and pyruvate oxidized was similar. The rate of glucose clearance also was significantly greater in the septic patients.

Comparing the response of these study participants to DCA, the septic patients significantly increased oxygen consumption, as measured by both indirect calorimetry (Table 3) and Fick dilution (Table 2). Because oxygen delivery was not altered significantly by DCA administration, the percent fractional oxygen extraction correspondingly increased (Table 2). In the healthy volunteers, no significant change in oxygen consumption as measured by indirect calorimetry was evident after DCA (Table 3). The septic patients had significant decreases in the arterial plasma concentrations of glucose, pyruvate, and lactate after DCA, whereas in the healthy volunteers, only pyruvate and lactate plasma concentrations decreased significantly (Table 3). There were marked decreases in glucose and pyruvate production after DCA in both septic patients and healthy volunteers. Furthermore, DCA increased significantly the percentage of glucose and pyruvate directed toward oxidation in both study groups. The rate of glucose clearance was not affected by DCA for either septic patients or healthy volunteers.

DISCUSSION

This study demonstrates that DCA can further increase the percentage of pyruvate oxidation and oxygen consumption while substantially lowering plasma lactate concentrations in patients with hyperdynamic sepsis. These findings strongly suggest the possibility that the accumulation of lactate during severe sepsis is not due to a deficiency in tissue oxygen availability. This conclusion is further supported by recent *in vivo* studies by Hotchkiss et al.,[9] in which septic rats were examined using phosphorus 31 nuclear magnetic resonance spectroscopy, [^{18}F] fluoromisomidazole, and microfluorometric enzymatic techniques. Using these methods, adequate cellular oxygenation and bioenergy availability was illustrated in septic animals. Furthermore, Jacobs and associates also found—using ^{31}P nuclear magnetic resonance spectroscopy—that although the phosphocreatine and inorganic phosphate ratio was reduced in muscle tissue from septic rats, the adenosine triphosphate/inorganic phosphate ratio and intracellular pH remained stable.[10] Such findings are not indicative of cellular hypoxia or ischemia. The results of these sophisticated animal studies, in conjunction with this human *in vivo* study using isotopic tracers, demonstrate that the longstanding hy-

pothesis linking lactic acidosis to anaerobic glycolysis may be unfounded during sepsis.

Extensive clinical findings also support the dichotomy between elevations in plasma lactate concentration in septic patients and their presumed impairment in oxygen use. For example, if the hypothesis is correct that plasma lactate concentrations are elevated in response to tissue oxygen deficiency, then increases in oxygen delivery should reduce lactate levels. However, numerous clinical surveys have failed to identify any consistent decrease in lactate concentrations in septic patients after volume resuscitation or blood transfusions.[11-13] An *in vivo* dog study by Curtis and Cain provides further evidence that plasma lactate concentrations during sepsis are not influenced by tissue hypoxia.[14] In this study, animals challenged with endotoxin and volume-resuscitated developed a progressive elevation in plasma lactate. However, lactate levels did not further increase during a 30-minute hypoxic challenge (fraction of inspired oxygen [FiO_2] = 0.12) while oxygen uptake increased. These authors also showed that DCA administration could reduce lactate levels without influencing oxygen use. Furthermore, Ronco et al. recently determined the critical oxygen delivery threshold for anaerobic metabolism in septic and nonseptic critically ill patients.[15] These authors demonstrated that the value for critical oxygen delivery is considerably lower than previously reported values using pooled group data, and that this critical oxygen delivery was not altered by sepsis. Ronco et al.[15] further showed that the increased lactate concentrations in these critically ill patients was not associated with an increased critical oxygen delivery or an impairment in tissue oxygen extraction.

Another important finding of this study is that in comparison to healthy controls, sepsis was associated with a 450% elevation in the rate of pyruvate oxidation and a proportional increase in the rate of pyruvate production. In contrast to the conclusions from previous studies, no limitation in carbohydrate oxidation appears evident in these critically ill patients.[16,17] Thus, pyruvate dehydrogenase activity does not appear to be impaired during sepsis. Previous reports by Vary and associates[4] of a decrease in pyruvate dehydrogenase enzyme activity in septic animal tissue does not appear to translate to an impairment in pyruvate oxidation *in vivo*. The findings of this study are similar to that reported by Wolfe et al.[3] in severe burn patients, in which the rate of pyruvate production and oxidation increased proportionately by approximately 300% over volunteer controls. The results of Wolfe et al.[3] and the current study strongly suggest that elevations in lactate production during critical illness from either sepsis or burns is linked to an acceleration of pyruvate production and not to any preferential shunting of pyruvate to lactate because of hypoxia or an impairment of pyruvate dehydrogenase activity.

Crabtree and Newsholme[18] observed accelerated rates of glycolysis in rapidly dividing cells. By applying quantitative principals of control to branched metabolic pathways, these researchers suggested that the increase in glucose use was not only to generate more energy or biosynthetic precursors per se but to heighten the sensitivity and response of the entire metabolic process. Their hypothesis also may be applicable in explaining the increased flux of nearly every metabolic pathway in critically ill patients. Thus, the increased glucose/pyruvate flux observed in this study of septic patients and by Wolfe et al.[3] in burn patients may be an adaptive mechanism for improved sensitivity of the metabolic response and to provide for more efficient generation of energy and biosynthetic precursors. The increased production of lactate in critically ill patients may result simply as a byproduct of the overall acceleration in glycolysis. The accumulation of lactate also may have physiologic benefits in septic patients, in whom the acidic environment may aid in the disassociation of oxygen from hemoglobin and thus improve tissue oxygen delivery.

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